Oncologic Drugs Advisory Committee
May 3, 2004

Genasense™
(oblimersen sodium) Injection
for Advanced Melanoma in Combination with Dacarbazine (DTIC)

CC-1

Genasense Introduction

Loretta M. Itri, MD
Chief Medical Officer
Genta Incorporated

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Agenda for Today's Meeting

Introduction	Loretta M. Itri, MD
Melanoma Overview	John M. Kirkwood, MD
Study GM301	Loretta M. Itri, MD
Clinical Benefit Summary	Frank Haluska, MD, PhD

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Speakers

Frank Haluska MD, PhD
Chairman, CALGB Melanoma Committee
Harvard Medical School &
Massachusetts General Hospital

John Kirkwood, MD
Chairman, ECOG Melanoma Committee
Professor and Vice Chairman
Department of Medicine
University of Pittsburgh Cancer Institute

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Experts Available for Q & A

Clinical

Sanjiv Agarwala, MD
Associate Director, Melanoma Program
University of Pittsburgh Cancer Institute

Agop Bedikian, MD
Professor of Medicine
Department of Melanoma Medical Oncology
MD Anderson Cancer Center

Paul Chapman, MD
Associate Attending, Clinical Immunology
Head, Melanoma Section
Memorial Sloan-Kettering Cancer Center

Robert Conry, MD
Associate Professor of Medicine
Hematology/Oncology
University of Alabama

Peter Hersey, MD, FRACP, D. Phil
Faculty of Health
University of Newcastle, NSW

Evan Hersh, MD
Professor of Medicine, Microbiology & Immunology
University of Arizona Cancer Center

Statistical

Janet Wittes, PhD
Statistics Collaborative Inc
Washington D.C

Radiology

Robert R. Ford, MD
Founder, Co-CEO
Chief Medical Officer, RadPharm
Princeton, NJ

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Metastatic Melanoma

John Kirkwood, MD

Chairman, ECOG Melanoma Committee
Professor and Vice Chairman
Department of Medicine
University of Pittsburgh Cancer Institute

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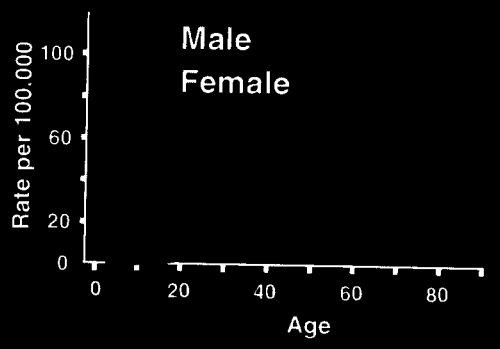
Malignant Melanoma
2004 Incidence

- 4% of new cancers
  ↑5 % per year
- 55,100 new cases
  7,910 deaths
- Mortality increase greatest for males > age 60
- Productive life-year loss exceeds prostate cancer



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Advanced Melanoma
Approved Agents

- Three agents approved
  - No controlled studies
  - No survival benefit
  - Substantial toxicity
- Basis of approval
  - Hydroxyurea (1967) — response rate
  - DTIC (1975) — response rate (7-13%)*
  - IL-2 (1998) — durable response

* Eggermont and Kirkwood EJC 2004

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IL-2 in Melanoma
Substantial Evidence of Efficacy

N=270

Study design	Pooled, non-randomized
Eligibility	Highly selected
Median age	42 yrs
Efficacy	Durable response
Toxicity	Cardiac; renal; hypotension; fluid overload; sepsis

CC-9

IL-2 in Melanoma
Substantial Evidence of Efficacy

N=270

	n	(%)
Overall response*	43	(16)
CRs	17	(6)
Surgical CRs	5	
PRs	26	(10)
Survival of CRs		
Median	5+ yrs	
Number alive	10	(3.7)
Drug-related mortality	6	(2)

*non-RECIST

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Efficacy Endpoints
Recent Melanoma Studies

Study (Yr Published)	No Pts	Response Rate	Complete Response Rate	Durable Response Rate	Progression Free Survival
IL-2 (1999)	270	NC	NC	NC	NC
Dartmouth vs DTIC (1999)	240	NS	NS	NR	NS
Biochemo vs chemo (E3695) (2003)	416	NS	NS	NR	NS
Chemo/IFN vs Biochemo (EORTC) (2003)	363	NS	NS	NS	NS
Fotemustine vs DTIC (2004)	229	NS	NS	NR	NS

NS=Not significant: NR=Not reported: NC=No comparator

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Temozolomide
Efficacy Results

	P-value
Overall response	NS
Complete response	NS
Durable response	NR
Progression free survival	0.002

CC-12

Advanced Melanoma
Conclusions

- Single-agent DTIC remains the reference
- Combination chemotherapy is not superior to DTIC alone
- High-dose IL-2 can induce durable responses
  - Response rate is low
  - Requires hospitalization
  - Toxicity can be severe
  - Clinical use limited to young patients with good performance status

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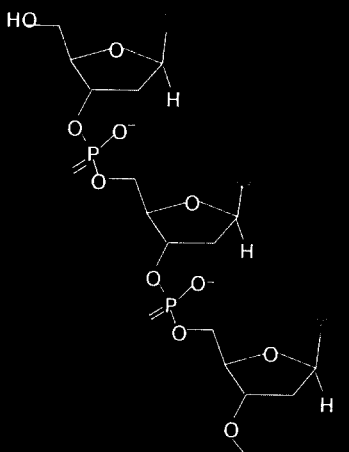
Advanced Melanoma
Conclusions

Advanced melanoma is a drug-refractory neoplasm

New treatment options are needed

CC-14

Genasense
(Bcl-2 antisense; G3139; oblimersen sodium)



- Antisense: protein knockout strategy
- Bcl-2: major anti-apoptotic protein; highly expressed in melanoma
- Strategy: block production of Bcl-2
- Goal: enhance efficacy of chemotherapy

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Genasense Decreases Bcl-2 Protein in Advanced Melanoma

Serial Biopsies

Dose: 6.5 mg/kg/d x 5 days

Jansen et al.. Lancet 2000

CC-16

GM301: Randomized Phase 3 Trial of Dacarbazine with or without Bcl-2 Antisense (G3139; oblimersen sodium) in Patients with Advanced Malignant Melanoma

CC-17

Genasense in Advanced Melanoma
Phase 3 Trial

- Largest randomized trial (N=771)
- Open-label, multicenter (139 sites; 9 countries)
- Primary endpoint
  - Overall survival
- Secondary endpoints
  - Progression free survival
  - Antitumor response (RECIST), computer calculated
  - Durable response ($\geq$ 6 mos)
  - Safety

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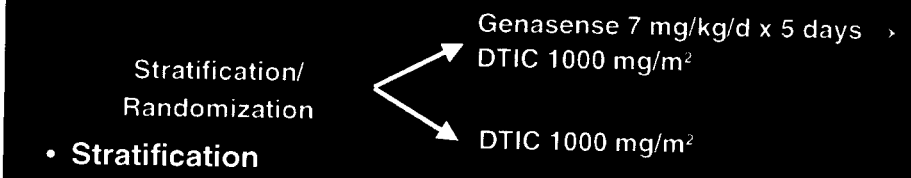
Genasense in Advanced Melanoma
Phase 3 Trial



- Stratification
  - ECOG PS (0 versus 1-2)
  - Liver metastasis
  - LDH
- Cycles Q 21 days (up to 8 cycles)
- Restaging evaluations Q 2 cycles
- No cross-over
- Follow-up for 2 years
- Genasense arm only: extension protocol GM214

CC-19

Statistical Assumptions

- Median survival
  - DTIC = 6 mos
  - Genasense/DTIC = 8 mos
- N = 750 pts (375 per group)
- 90% power; alpha = 0.05 (2-sided)
- Constant accrual: 30 pts/mo
- Event-driven analysis: ≥ 508 deaths

CC-20

Study Demographics
N = 771

	Genasense/ DTIC (n = 386)	DTIC (n = 385)	P-Value
Age (median, yrs)	59	60	NS
Age group	n (%)	n (%)	
< 65	239 (62)	241 (63)	
≥ 65	147 (38)	144 (37)	
≥ 75	47 (12)	54 (14)	
Gender			NS
Female	150 (39)	132 (34)	
Male	236 (61)	253 (66)	

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Baseline ECOG Performance Status

	Genasense/ DTIC (n=378)	DTIC (n=383)
0	207 (54.8)	220 (57.4)
1	146 (38.6)	132 (34.5)
2	24 (6.3)	29 (7.6)
3	1 (0.3)	2 (0.5)

CC-22

Melanoma History
N = 771

		Genasense/ DTIC	DTIC	P-Value
Time from diagnosis (median, mos)		29.5	26.4	NS
LDH/disease distribution	(AJCC)	n (%)		NS
Non-visceral and non-↑ LDH	(M1a)	61 (15.8)	50 (13.0)	
Lung and non-↑ LDH	(M1b)	93 (24.1)	75 (19.5)	
Visceral other than lung, or ↑ LDH	(M1c)	226 (58.5)	257 (66.8)	
Prior immunotherapy		156 (40.4)	142 (36.9)	NS

CC-23

Randomization and Treatment
N = 771

	Genasense/ DTIC n (%)	DTIC n (%)
Randomized	386 (100)	385 (100)
Randomized and treated	371 (96.1)	360 (93.5)
Randomized, not treated	15 (3.9)	25 (6.5)

CC-24

Cumulative DTIC Dose
Equivalence in Treatment Arms

	Genasense / DTIC mg/m² (n=365)	DTIC mg/m² (n=360)	P-value
Mean	3418	3372	NS
Median	2055	2008	

CC-25

GM301 Efficacy

CC-26

Efficacy Summary
Intent-To-Treat

	Genasense/ DTIC (n=386)	DTIC (n=385)	Hazard Ratio	P-Value
Overall survival (median, mos)	9.1	7.9	0.89	0.18
Progression free survival (median, days)	74	49	0.73	0.0003
Overall response n (%)	45 (11.7)	26 (6.8)	-	0.019
Durable response n (%)	13 (3.4)	5 (1.3)	-	0.057

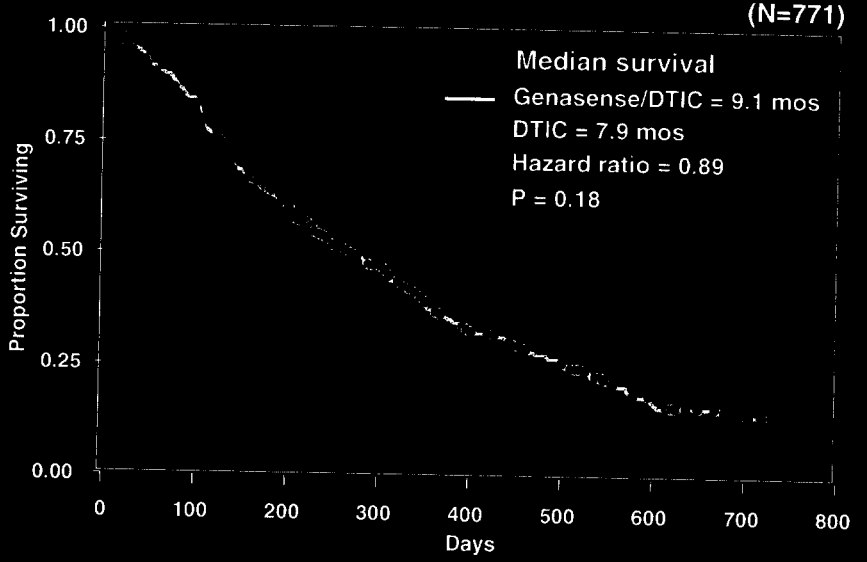
CC-27

ODAC Review Considerations

- Response rate concordance
- Impact of interval assessments on PFS
- Impact of missing data on PFS
- Baseline differences in prognostic factors
- Influence of non-US sites on response rate

CC-28

Overall Survival
Intent-to-Treat



CC-29

Antitumor Response
Intent-to-Treat: NDA

	Genasense/ DTIC (n=386) n (%)	DTIC (n=385) n (%)	P-Value
Objective response	45 (11.7)	26 (6.8)	0.019
Complete	5 (1.3)	2 (0.5)	
Partial	40 (10.4)	24 (6.2)	
Stable disease	116 (30.1)	106 (27.5)	
Progressive disease	152 (39.4)	178 (46.2)	
Inevaluable	73 (18.9)	75 (19.5)	

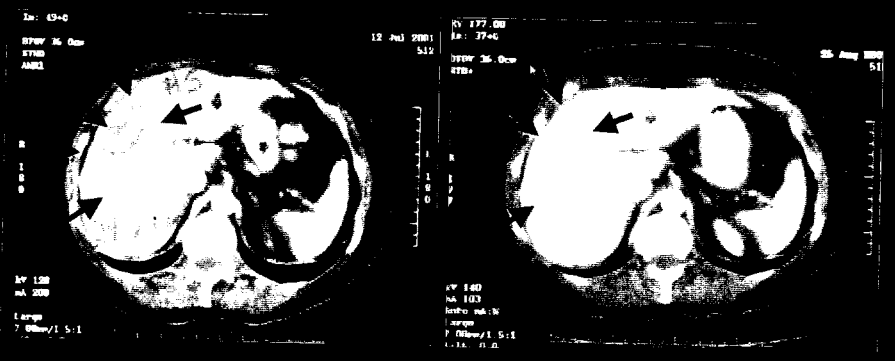
CC-30

RadPharm Procedures

- Mandatory review of 71 responding patients only
- Assessment according to RECIST
- Reviewers blinded to:
  - Treatment
  - Clinical information
  - Site target lesion determination
  - Site measurements

CC-31

Subject 205-02: Complete Response
Survival 33+ Months



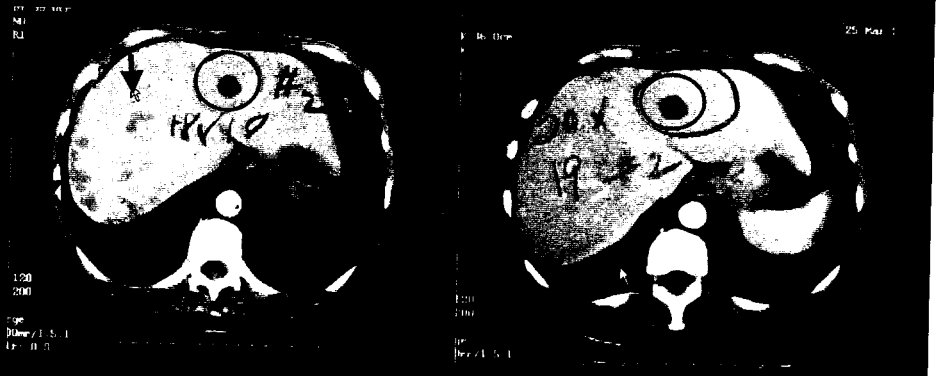
Baseline

Post Therapy

CC-32

Subject 205-02
Liver Cyst as Target Lesion PR by RadPharm

Survival 33+ Months

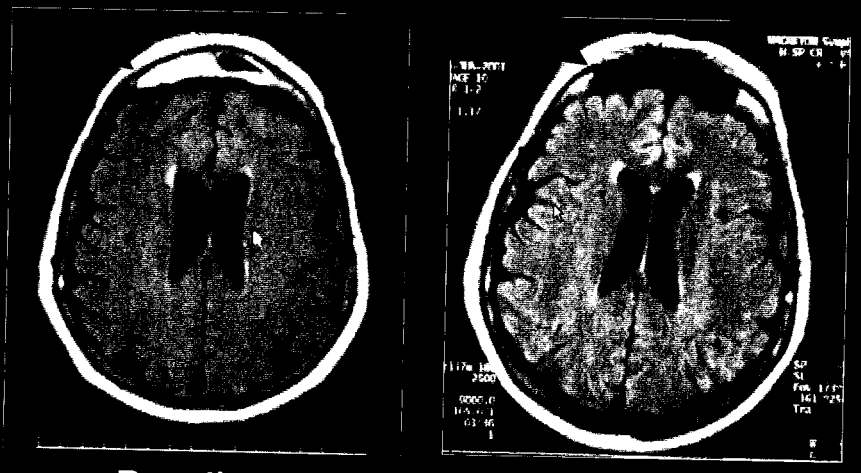


Baseline

Post Therapy

CC-33

Subject 907-02
Unconfirmed Response

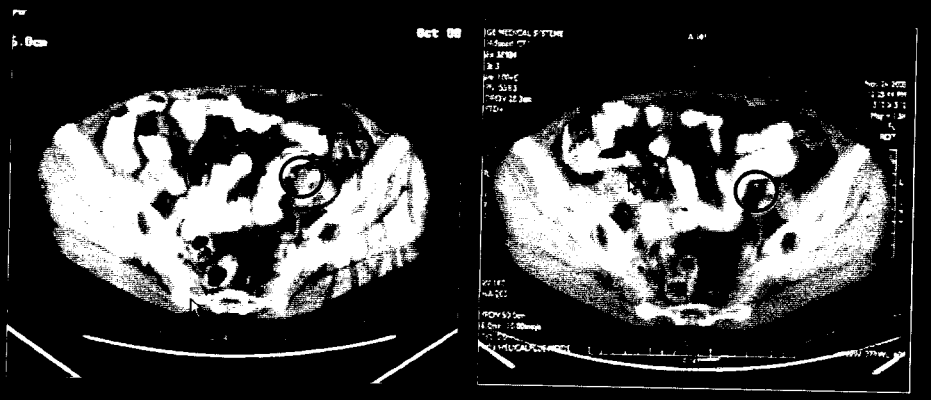


Baseline

Post Therapy

CC-34

Subject 908-16
Ongoing Duration of Clinical Benefit: 18+ month

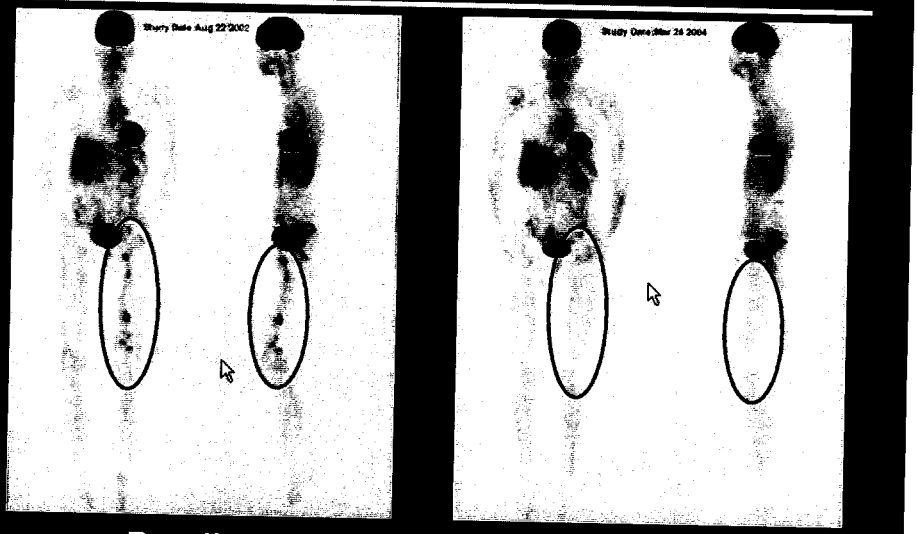


Baseline

Post Therapy

CC-35

Subject 908-16



Baseline

Post Therapy

CC-36

RadPharm Response Concordance

- 71 responding subjects: 60 evaluable
- Consistent assessment for 52 of 60 (87%) subjects
  - 38 "concordant" (PR=PR) - 63%
  - 2 consistent responders (CR↔PR)
  - 8 consistent on 1 evaluation
  - 4 explained by medical history
- Odds ratio consistent Radpharm (1.91) vs CRF (1.82)

CC-37

FDA Review Update
Timing and Methods

- FDA request (2/04) for TTP verification by RadPharm
  - 80 additional cases (40/arm)
  - New responses identified in follow-up period
- Prompted review of:
  - All follow-up pts with RECIST PR or CR ≥ 1 timepoint
  - All pts ending treatment phase with ≥ SD
  - No intervening therapy

* Submitted to FDA 4/9/04

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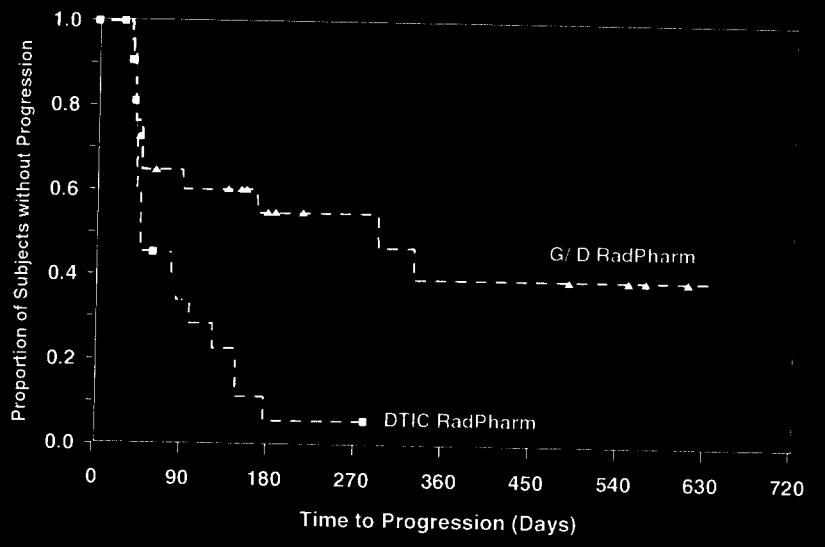
Comparison of Time to Progression (TTP) Between CRF & RadPharm Data



CC-39

Antitumor Response
Intent-to-Treat: FDA Review Update

	Genasense/ DTIC (n=386) n (%)	DTIC (n=385) n (%)	Nominal P-Value
Objective response	48 (12.4)	26 (6.8)	
Complete*	11 (2.8)	2 (0.5)	0.02
Partial	37 (9.6)	24 (6.2)	
Stable disease	113 (29.3)	106 (27.5)	

* Includes 3 surgical CRs in Genasense arm

CC-40

Complete Responders
FDA Review Update

		Genasense/DTIC n=11	DTIC n=2
Male/Female		6/5	0/2
Median age (range)		62 (49-75)	52 (39-72)
ECOG PS	0	8	1
	1	3	1
LDH	Normal	7	1
	Elevated	4	1
AJCC	M1a	5	0
	M1b	2	0
	M1c	4	2

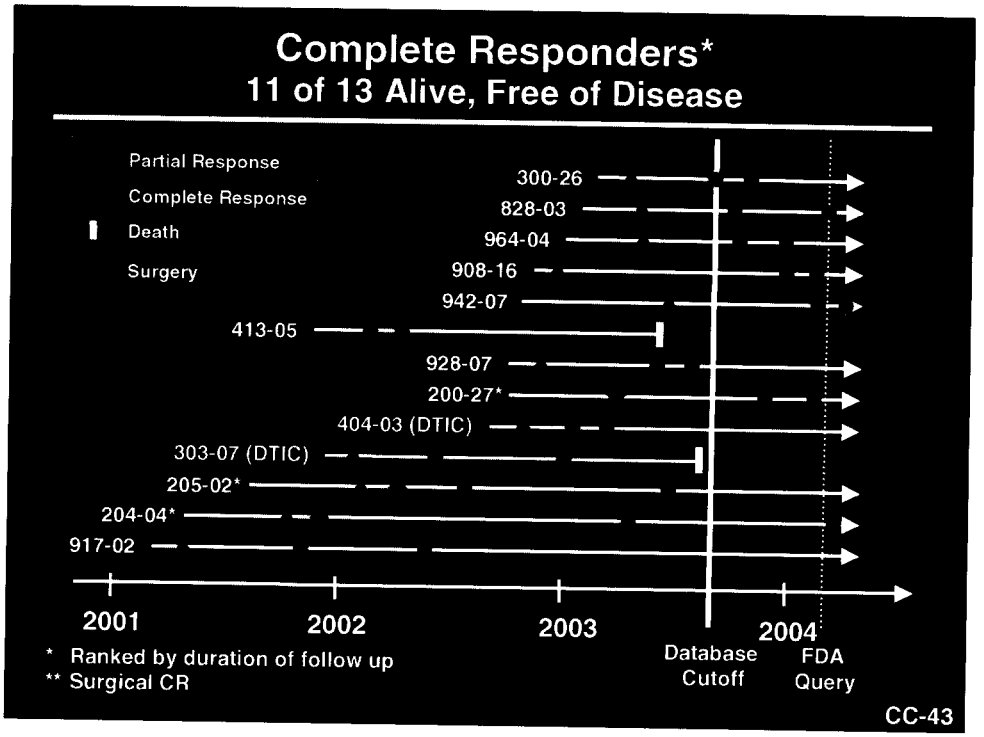
CC-41

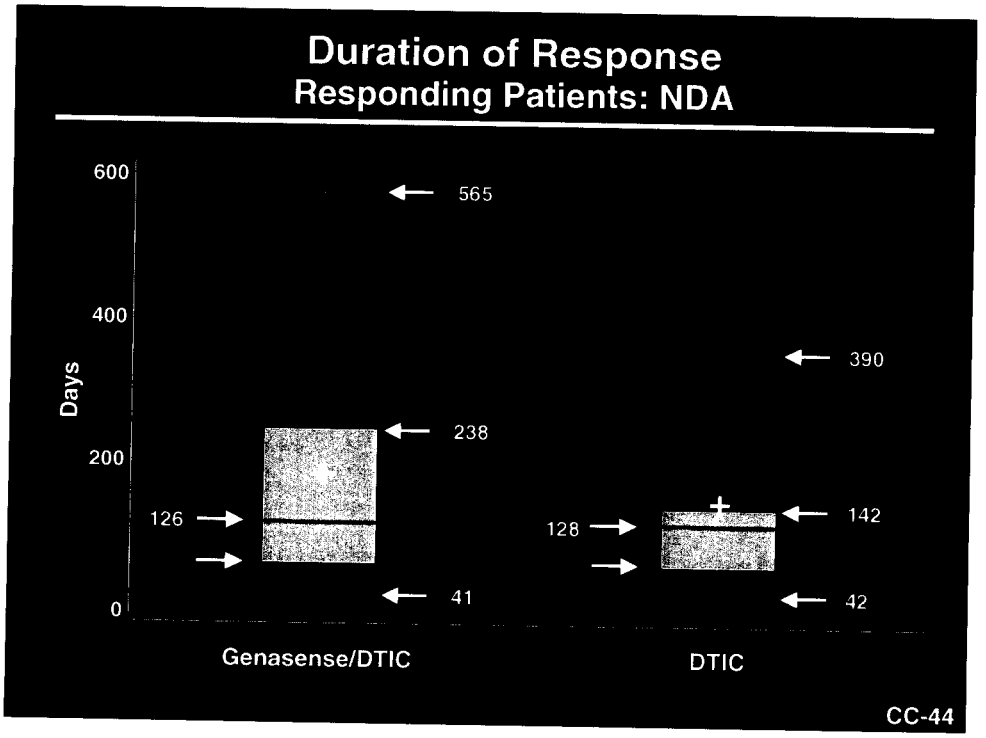
Complete Responders Survival
FDA Review Update

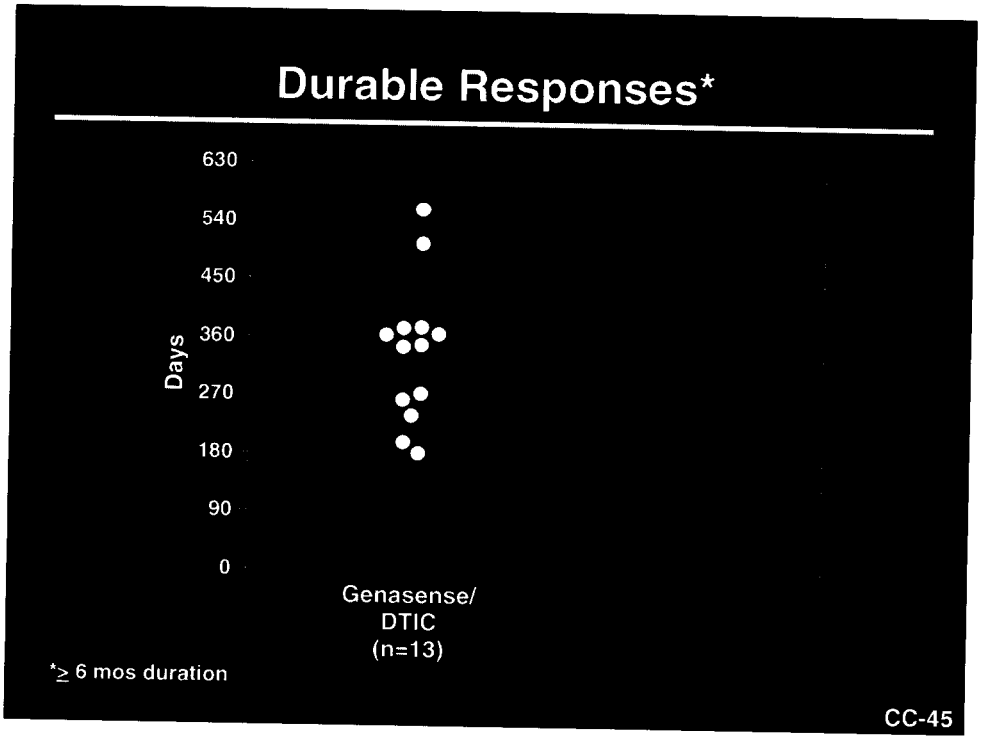
	Genasense/ DTIC n=11	DTIC n=2
Survival** (mos) Range (15-38)	38+, 36+*, 33+*, 20, 19+*, 19+, 19+, 18+, 16+, 15+, 15+,	21, 19+,

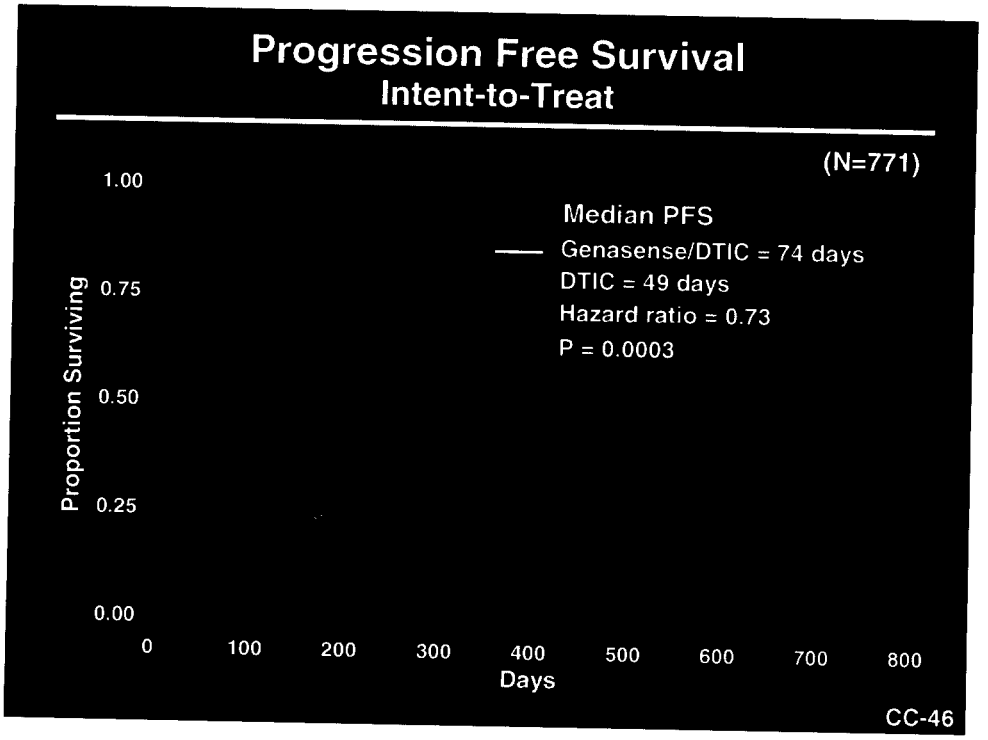
* Surgically maintained
**Survival from randomization to death or last follow-up March '04

CC-42

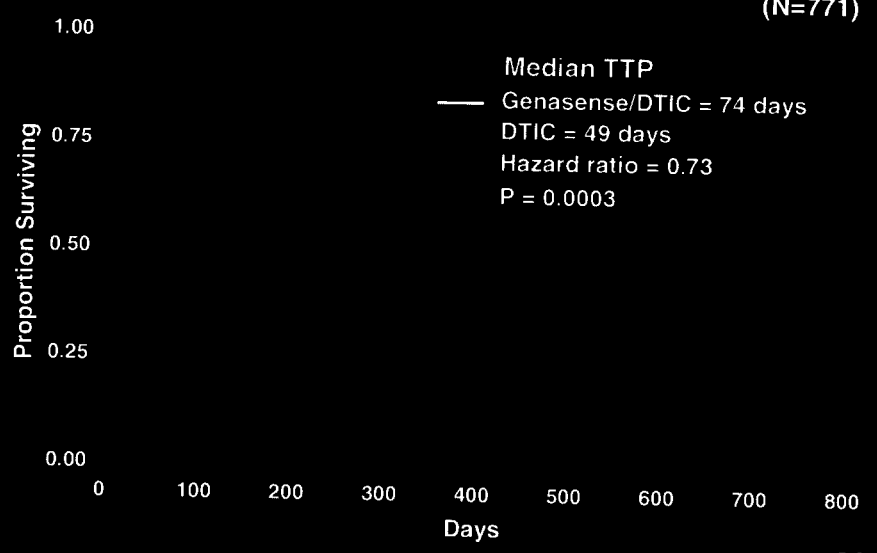

Complete Responders*
11 of 13 Alive, Free of Disease
Partial Response
Complete Response
Death
Surgery
300-26
828-03
964-04
908-16
942-07
413-05
928-07
200-27*
404-03 (DTIC)
303-07 (DTIC)
205-02*
204-04*
917-02
2001
2002
2003
2004
Database Cutoff
FDA Query
* Ranked by duration of follow up
** Surgical CR
CC-43


Duration of Response
Responding Patients: NDA
600
400
200
0
Days
565
390
238
126
128
142
41
42
Genasense/DTIC
DTIC
CC-44


Durable Responses*
630
540
450
360
270
180
90
0
Days
Genasense/
DTIC
(n=13)
*≥ 6 mos duration
CC-45


Progression Free Survival
Intent-to-Treat
(N=771)
1.00
0.75
0.50
0.25
0.00
Proportion Surviving
Median PFS
Genasense/DTIC = 74 days
DTIC = 49 days
Hazard ratio = 0.73
P = 0.0003
0
100
200
300
400
500
600
700
800
Days
CC-46

Time to Progression
Intent-to-Treat



CC-47

Progression Free Survival
Sensitivity Analyses (Genta)

Method	Hazard Ratio	P-value
Time to progression (TTP)	0.73	0.0003
Time to treatment failure	0.78	0.0008
Average of prior and post-observation data for missing data	0.74	0.0004
PFS censored 60 days after last lesion measurement	0.75	0.0010
PFS censored at end of treatment phase	0.73	0.0005
Earliest date used in a given cycle	0.73	0.0002
Nontarget lesion used to determine progression	0.75	0.0006
FDA requested analysis, applying 50% rule	0.75	0.0006
By cycle analysis	0.84	0.045
Assumed PD back to scheduled visit when visit late	0.78	0.0046
Assumed PD back to scheduled visit when visit was late, including censored patients	0.83	0.0276

CC-48

Progression Free Survival
Interval Censoring Analyses (FDA)

Method	Hazard Ratio	P-Value
Approach 1, assessment schedule bias	NR	0.016
Approach 2, assessment schedule and missing data bias	NR	0.026
Approach 3, assessment schedule and missing data bias	NR	0.031
Approach 4, assessment schedule and missing data bias	NR	0.141

CC-49

Patient 203-03

		Target lesion measurement (mm)							Non-target lesion evaluation			
Cycle	Day	#1	#2	#3	#4	#5	#6	#7	Brain	Liver	Lung	Other organ site
Baseline	1	53	32	35	50	21	31	31	Absent	Present	Present	Absent
Cycle 2	47	44	27	25	51	25	28	28	-	Present, w/o progression	Present, w/o progression	Confirmation of absence
Cycle 4	89	35	25	17	37	22	23	26	-	Present, w/o progression	Present, w/o progression	Confirmation of absence
Cycle 6	131	30	29	15	34	21	19	26	-	Present, w/o progression	Present, w/o progression	Confirmation of absence
Cycle 8	173	33	41	16	31	23	19	29	-	Present, w/o progression	Present, w/o progression	Confirmation of absence
F/U1	229	60	48	25	39	23	20	29	-	Present, w/o progression	Present, w/o progression	Confirmation of absence

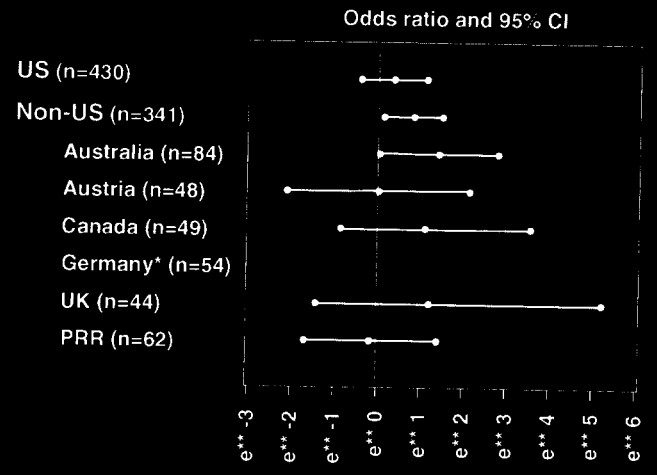
CC-50

PFS or Response Results Not Affected by Baseline Differences

	Progression free survival		Response	
	Hazard Ratio	P-Value	Odds Ratio	P-Value
Planned analysis	0.73	0.0003	1.82	0.019
Adjusted for:				
Age	0.73	0.0003	1.83	0.019
Gender	0.74	0.0005	1.80	0.023
AJCC	0.77	0.0029	1.69	0.044

CC-51

ITT: Response Rate By Country
No Difference US vs Non-US



*Germany: 2 responders on G/D: 0 responders on DTIC
**Natural log-base scale
PRR: Poland, Romania, Russia

CC-52

Review Considerations

Radiographic non-concordance	Concordance documented
Effect of interval assessments of PFS	Benefit maintained with aggressive sensitivity analyses
Impact of missing data on PFS	Benefit maintained with aggressive sensitivity analyses
Baseline demographic differences	No effect on endpoints
Response rate driven by Non-US sites	Benefit observed US and Non-US

CC-53

GM301 Safety

CC-54

Adverse Events

- Adverse events increased overall
- No new or unexpected events
- Increased incidence of
  - Fever
  - Neutropenia
  - Thrombocytopenia
  - Catheter-related complications
- Regular independent DSMB review of AEs revealed no safety concerns

CC-55

Thrombocytopenia and Bleeding
Treatment Emergent Adverse Events

	Genasense/DTIC (N=371) n (%)	DTIC (N=360) n (%)
Grade 3-4 thrombocytopenia	58 (15.6)	23 (6.4)
Serious thrombocytopenia	15 (4.0)	4 (1.1)
Clinical consequence		
Grade 3-4 bleeding	8 (2.2)	11 (3.1)
Serious bleeding	5 (1.3)	9 (2.5)
Serious bleeding with thrombocytopenia	3 (0.8)	3 (0.8)
Platelet transfusions	14 (3.8)	9 (2.5)
No. Units	53	57

CC-56

Neutropenia and Infection
Treatment Emergent Adverse Events

	Genasense/ DTIC N=371 n (%)	DTIC N=360 n (%)
Grade 3-4 neutropenia	79 (21.3)	45 (12.5)
Serious neutropenia	8 (2.2)	1 (0.3)
Clinical consequence		
Grade 3-4 neutropenic infection	16 (4.3)	10 (2.8)
Serious neutropenic infection	11 (3.0)	8 (2.2)

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Administration Related Complications
Treatment Emergent Adverse Events

	Genasense/ DTIC (N = 371) n (%)	DTIC (N = 360) n (%)
Injection site infection	15 (4.0)	0 (0.0)
Injection site reaction	0 (0.0)	8 (2.2)
Thrombotic events	8 (2.2)	1 (0.3)
Pump misprogramed	2 (0.5)	NA

- SC Dosing formulation under development

CC-58

Treatment Emergent Adverse Events

	Genasense/ DTIC (N = 371) n (%)	DTIC (N = 360) n (%)
AE leading to discontinuation	69 (18.6)	39 (10.8)
AE with outcome of death	32 (8.6)	33 (9.2)
Death ≤ 30 days from last dose of study drug	29 (7.8)	25 (6.9)

CC-59

Genasense/DTIC in Advanced Melanoma

- Large, randomized study:
  - Well conducted
  - Internally consistent
  - Demonstrated compelling results
- ODAC considerations addressed
- Clinical benefit demonstrated

CC-60

Clinical Benefit Summary

Frank Haluska, MD, PhD

Co-Chairman, CALGB Melanoma Committee

Harvard Medical School &

Massachusetts General Hospital

Boston, MA

CC-61

Factors Bearing on Approval

- Sponsor failed to meet the primary endpoint of the study
- But significant clinical benefit is strongly suggested by secondary measures of effectiveness

CC-62

Genasense/DTIC
Clinical Benefits

- Overall response rate: Improved
  - 11.7 vs 6.8%
- Complete response: Improved
  - 11 vs 2
- Progression-free survival Improved
  - 74 vs. 49 days
  - Hazard ratio of 0.73

CC-63

Efficacy Endpoints
Recent Melanoma Studies

	No. Pts	Response Rate	Complete Response	Progression free survival
Dartmouth vs. DTIC (1999)	240	NS	NS	NS
Bio-chemo vs. chemo (E3695) (2003)	416	NS	NS	NS
Chemo/IFN vs Biochemo (EORTC) (2003)	363	NS	NS	NS
Fotemustine vs. DTIC (2004)	229	NS	NS	NS
Genasense/DTIC vs DTIC (2004)	771	P=0.02	P=0.02	P=0.0003

NS: Not Significant

CC-64

Genasense/DTIC
Clinical Benefits

- Patients value responses
- Patients value complete responses
- Recent approval history and data on responses to targeted therapies underscore a clinical benefit in subset of patients
- Patients value time free of disease progression, even if that time is short

CC-65

Genasense/DTIC
Safety Summary

- No new or unexpected adverse events
- No difference in treatment-related deaths
- Increase in fever, neutropenia, thrombocytopenia, and catheter-related complications
- But Genasense still better-tolerated than other tested therapies

CC-66

Genasense in Melanoma

- Melanoma is refractory to current front line therapy
- Genasense is safe and effective when combined with DTIC to treat stage IV melanoma
- In other words: the data show that this combination works, and we need drugs that work for advanced melanoma

CC-69

Oncologic Drugs Advisory Committee
May 3, 2004

Genasense™
(oblimersen sodium) Injection
for Advanced Melanoma in Combination with Dacarbazine (DTIC)

CC-70